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Fixed-dose vasopressin does not ensure a predictable physiological response

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1. Introduction

Vasopressin has become a widely used adjunct vasopressor in the management of septic shock and other forms of vasodilatory circulatory failure [1]. Current clinical practice guidelines recommend vasopressin as a fixed-dose infusion, most commonly at 0.03 U/min [2], although some allow for a slightly broader range between 0.01 and 0.04 U/min [3–5]. This approach aims to reduce catecholamine exposure and restore vascular tone [6].

At the same time, this strategy implies that a standardized infusion rate produces a consistent physiological effect across patients—an assumption that is difficult to reconcile with the biological diversity observed in critical illness. This inconsistency reflects a form of dose–effect uncoupling, in which a time-based infusion (units/min), rather than a weight-normalized dose (units/kg/min), does not reliably translate into a predictable hemodynamic or vascular response.

Unlike catecholamines such as norepinephrine, which are continuously adjusted to achieve predefined hemodynamic targets, vasopressin is often initiated at a fixed rate that remains unchanged [2]. As a result, identical absolute amounts of a potent vasoactive hormone are delivered to patients who may differ markedly in body size, circulating volume, vascular responsiveness, and underlying pathophysiology.

For example, an infusion rate of 0.03 U/min delivers the same quantity of vasopressin to a 50-kg patient as to a 120-kg patient (Fig. 1). When expressed relative to body weight, this represents an approximate twofold difference in effective dose (U/kg/min). Consequently, the resulting vascular exposure and receptor activation are unlikely to be equivalent. Additional factors common in critical illness—including inflammation, endothelial dysfunction, and altered signaling pathways—further influence how this exposure is translated into a physiological response [6]. The hemodynamic response to vasopressin may also be modulated by contextual factors at the time of initiation, including the concurrent norepinephrine dose, systemic acid–base status (pH), and serum lactate levels, all of which reflect shock severity and may alter vascular responsiveness [7].

The use of vasopressin in septic shock is grounded in the observation that endogenous levels may become insufficient during prolonged vasodilatory states [8]. Although the concept of "relative vasopressin deficiency" provides a coherent rationale for exogenous administration, it represents a simplification of a complex neuroendocrine system. Vasopressin acts through multiple receptor pathways with vascular, renal, and endocrine effects, and its impact is shaped by receptor expression, endothelial function, nitric oxide–mediated vasoplegia, and baseline hormonal conditions [6,9].

The widespread adoption of this dosing strategy is closely linked to the structure of landmark clinical trials. In the Vasopressin and Septic Shock Trial (VASST), vasopressin was administered at 0.01–0.03 U/min alongside norepinephrine [3]. This dosing scheme was designed to ensure safety and standardization rather than to define an optimal physiological or pharmacodynamic dose. Over time, these protocol-driven limits have been incorporated into clinical practice and are frequently interpreted as physiologically meaningful thresholds, despite their methodological origins.

Clinical experience underscores the variability in response to vasopressin. Some patients exhibit a clear reduction in norepinephrine requirements, suggesting improved vascular tone, whereas others show minimal change at identical infusion rates [3,4,6,10]. This variability reflects the non-uniform relationship between administered dose and observed effect and the interaction between vasopressin signaling, inflammatory mediators, and vascular function.

Another limitation of the fixed-dose paradigm is the reliance on arterial pressure as the primary indicator of therapeutic success. Although mean arterial pressure remains a central target in resuscitation, it represents only one aspect of circulatory support. An increase in arterial pressure does not necessarily indicate improved blood flow or tissue perfusion [11]. Vasopressin-induced vasoconstriction may increase macrocirculatory pressure while variably affecting cardiac output, impairing regional perfusion, or contributing to heterogeneous

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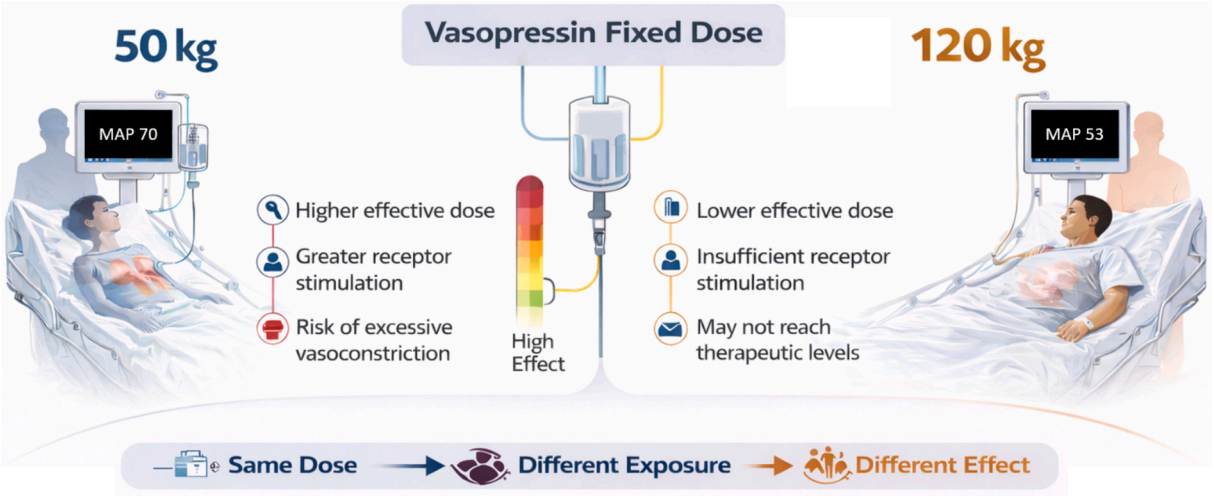

Fig. 1. Schematic representation of dose–effect uncoupling with fixed-dose vasopressin. Although the same infusion rate is administered, interpatient differences in body size and pharmacokinetic–pharmacodynamic determinants result in variable effective exposure (U/kg/min) and receptor activation. In lower-weight patients, higher effective dosing may increase vasoconstrictive effect, whereas in higher-weight patients, lower effective dosing may result in subtherapeutic exposure. This variability occurs independently of additional modifiers of vasopressin responsiveness commonly present in critical illness.

microvascular flow [3,6]. Without individualized physiological assessment, improvements in arterial pressure may be interpreted as evidence of global recovery when broader circulatory effects remain uncertain.

The concept of a fixed maximum dose introduces further complexity. A ceiling of 0.03–0.04 U/min may limit escalation in patients with insufficient response, while others may receive more vasoconstrictive stimulation than required. Studies comparing different vasopressin infusion rates have not consistently demonstrated clear differences in hemodynamic outcomes, supporting the notion that nominal dose alone does not determine physiological effect [5]. There is currently no clearly defined upper limit that reliably prevents ischemic complications, as the risk appears to depend more on individual vascular responsiveness than on the nominal dose itself.

These observations do not suggest that vasopressin should be administered without safety limits, nor that weight-based dosing is necessarily superior. Rather, they point to a broader issue in critical care pharmacology: protocol-defined doses are often pragmatic rather than physiologically optimized. The fixed-dose approach to vasopressin should therefore be viewed as a practical convention, not as evidence that a given infusion rate produces equivalent effects across patients.

Recent comparisons between weight-based and non–weight-based vasopressor strategies have focused on how dose is expressed or normalized [12]. While such approaches may influence aspects of drug exposure, they do not directly address the relationship between administered dose and biological effect. Weight-based dosing seeks to standardize exposure, whereas the present discussion challenges the assumption that a uniform dose produces a consistent response. These are distinct questions. Even when doses are normalized to body weight, variability in pharmacodynamic response may persist. Changing the denominator does not eliminate variability in the dose–response relationship.

Future research should move beyond whether vasopressin is used and instead identify the physiological conditions under which it is most effective. This may involve biomarkers, dynamic hemodynamic assessment, or integration of macro- and microcirculatory parameters to better define response. Such approaches could help determine whether vasopressin improves effective tissue perfusion or simply increases arterial pressure without restoring microvascular flow.

Until such tools are available, clinicians should be cautious in equating fixed dose with fixed effect. Vasopressin should be understood as a pharmacological intervention with variable impact across patients with vasodilatory shock. Recognizing this variability challenges the current paradigm and supports a shift toward physiology-guided and response-oriented vasopressor strategies in critical care.

Authors' contribution

CS-E wrote the entire manuscript.

CRediT authorship contribution statement

Carlos Sanchez-Escalante: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

Consent for publication

YES.

Ethics approval and consent to participate

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Declaration of competing interest

The author declare that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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